

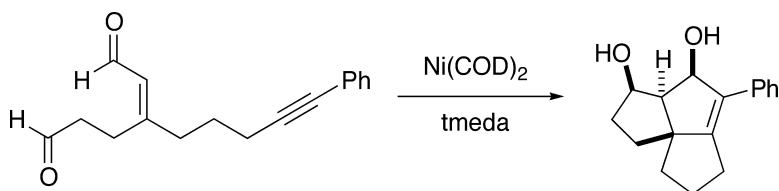
Article

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Cascade Cyclizations and Couplings Involving Nickel Enolates

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Abstract: A new strategy for effecting cascade cyclization processes using nickel enolates has been developed. Nickel enolates may be cleanly generated by the oxidative cyclization of an enal and alkyne with Ni(0), and the resulting enolate may be functionalized by a variety of alkylation processes. Partially and fully intramolecular versions of the process allow the rapid synthesis of complex polycyclics from simple achiral, acyclic precursors.

Introduction

Cascade metal-catalyzed cyclization processes have emerged as enormously useful methods for assembling complex polycyclic molecules from simple polyunsaturated precursors.¹ The iterative migratory insertion of various unsaturated groups into a reactive metal–carbon bond is often an important theme, and processes of this type may be coupled with carbonylation, transmetalation, and reductive elimination in well-timed sequences typically controlled by selective placement of reactive groups within a cyclization precursor.² Palladium-catalyzed methods involving the insertion of alkynes and 1,1-disubstituted alkenes, typically termed Heck cyclizations, have been very widely explored because the insertions proceed efficiently and involve σ -alkyl species that are not prone to reaction termination by β -hydride elimination.^{1,2}

Transition metal enolates have been well documented in many contexts, and their modes of reactivity are diverse.³ Their preparation typically involves carbonyl enolization followed by addition to a metal electrophile,³ addition of metal anions to α -halocarbonyls,^{3a} conjugate additions or reductions of α,β -unsaturated carbonyls,⁴ and isomerization of allylic alcohols.⁵ Simple electrophilic alkylations and aldol additions,^{3a,g,4} arylations and alkenylations,⁶ and β -hydride elimination⁷ are among the many reactivity trends that are often seen for transition metal enolates. The diverse reactivity of transition metal enolates, if coupled with the complexity generation allowed by cascade cyclizations, would provide a powerful new strategy for complex molecule construction. Although conjugate reduction and con-

jugate addition entries to transition metal enolates have allowed notable progress toward this goal,⁴ we envisioned that polyunsaturated precursors could potentially provide access to very complex processes that involve the formation and alkylation of transition metal enolates as only two of numerous individual steps in elaborate metal-promoted polycyclizations. Herein, we describe our results toward this general goal.

Results and Discussion

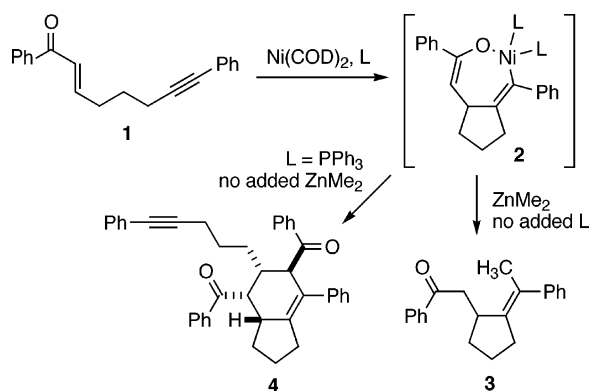
Our interest in the chemistry of nickel enolates stems from our recent work in the development of nickel-catalyzed cy-

[†] To whom correspondence regarding X-ray crystallographic determinations should be addressed.

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Scheme 1



clizations of alkyne enones and organozincs.⁸ For example, when enone substrate **1** is treated with $\text{Ni}(\text{COD})_2$ in the presence of dimethylzinc, product **3** is cleanly produced (Scheme 1).⁹ We speculated that metallacycle **2**, which possesses a nickel enolate motif, was a likely intermediate in this transformation. To study the mechanism of this process, we attempted to independently prepare the proposed metallacycle simply by treating enone **1** with a stoichiometric quantity of $\text{Ni}(\text{COD})_2/\text{PPh}_3$ (1:2) in the absence of dimethylzinc. However, this catalytic system led to the quantitative dimerization of the alkyne enone to afford product **4** as a single isomer (Scheme 1).¹⁰

Recognizing that metallacycle **2** could potentially serve as a common intermediate leading to either alkylative cyclization product **3** or dimer **4** depending on the reaction conditions, we reasoned that stabilization of metallacycle **2** with a bidentate ligand would suppress uptake of a second equivalent of enone and allow isolation of the reactive metallacycle. This expectation was indeed correct, and treatment of alkyne enone **5** with stoichiometric $\text{Ni}(\text{COD})_2/\text{tmeda}$ (1:1) cleanly afforded the structurally well-defined Ni(II) enolate **6** as the major product after recrystallization (Scheme 2).¹¹ Both solid-state and solution characterization data were fully consistent with the η^1 *O*-enolate structure for metallacycle **6**.¹¹

Although the preparation of analytically pure metallacycle **6** required careful recrystallization, we were interested in examining the reactivity of the crude metallacycle which was easily prepared in solution. Thus, after treatment of alkyne enone **5** with $\text{Ni}(\text{COD})_2/\text{tmeda}$ for 1 h at room temperature, the resulting red solution was quenched with either methanol or dilute aqueous acid. Surprisingly, this one-pot procedure directly afforded bicyclooctenol **7** in 82% yield (eq 1).¹² This process formally constitutes a reductive [3+2] cycloaddition with excellent control of stereochemistry. Although many examples of [3+2] cycloadditions have appeared,¹³ most examples require specialized substrate classes that cannot be carried through

Scheme 2

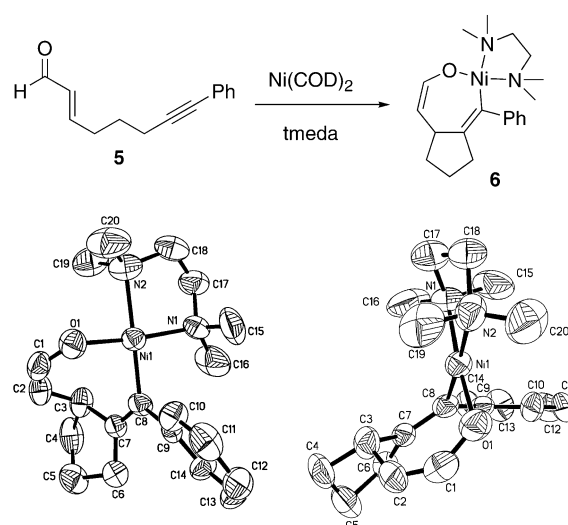


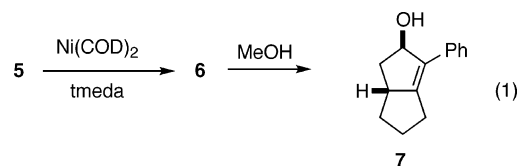
Table 1

Table 1 illustrates the reaction of alkyne-enone **8** with $\text{Ni}(\text{COD})_2$ and tmeda to form products **9**, **10**, and **11**.

entry	<i>n</i>	X	R ¹	R ²	% yield
1	1	CH ₂	H	Ph	9a (82) ^a
2	1	CH ₂	H	CH ₃	9b (72) ^a
3	2	CH ₂	H	Ph	9a' (40), 11a (18) ^a
4	1	CH ₂	H	COCH ₃	9c (15) ^a
5	1	CH ₂	H	SiMe ₃	9d (55) ^b
6	1	O	H	Ph	9e (78) ^a
7	1	CH ₂	Ph	Ph	9f (71) ^b
8	1	CH ₂	Ph	Ph	10a (53) ^a
9	1	CH ₂	Ph	CH ₃	10b (52) ^a
10	1	CH ₂	Ph	H	11b (27) ^a
11	1	CH ₂	Ph	SiMe ₃	9g (61) ^b
12	1	CH ₂	Ph	SiMe ₃	10c (61) ^a

^a Aqueous workup. ^b Methanol workup.

routine synthetic sequences and that are sometimes difficult to install into complex molecules. Thus, the participation of an easily installed α,β -unsaturated carbonyl as a three-carbon group that participates in a [3+2] cycloaddition is particularly attractive.



The scope of the process is illustrated by the following examples (Table 1). Enals are the most efficient participants in the reaction (entries 1–6), although aromatic enones are also satisfactory participants (7–12). With aromatic enones, the workup conditions are critical. For instance, in the cyclization

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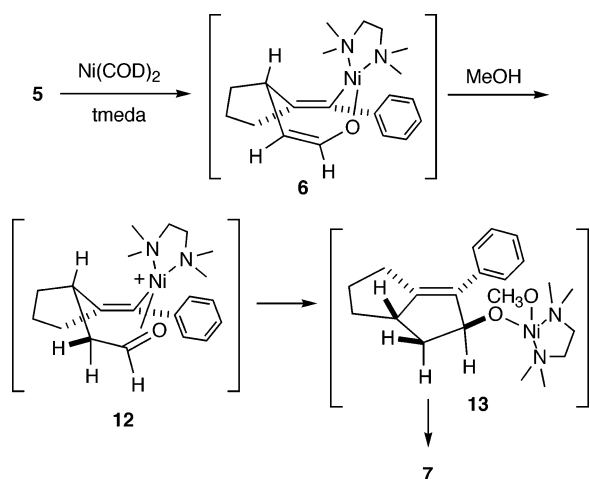
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Scheme 3



of a phenyl enone, product **9f** is generated in 71% yield if the reaction is quenched with methanol (entry 7). However, quenching with dilute acid leads to rearranged product **10a** derived from acid-catalyzed 1,3-transposition of the hydroxyl unit (entry 8). The products derived from enal cyclizations (entries 1–6) were less prone to rearrangement, and either aqueous or methanol workup was satisfactory for obtaining unrearranged products. Regarding substitution on the alkyne, aromatic (entries 1,3,6–8), aliphatic (entries 2,9), and silyl (entries 5,11,12) groups were tolerated in good yield. However, terminal alkynes (entry 10) and alkynoates (entry 4) were poor substrates. In the case of the terminal alkyne cyclization, monocyclic product **11b** was obtained (entry 10). A heteroatom was tolerated in the tether chain in good yield (entry 6), and six-membered cyclizations were also possible (entry 3).

We suggest that the mechanism of this novel process likely involves a selective monoprotonation of the nickel enolate of **6** upon workup while leaving the vinyl nickel unit intact (Scheme 3). Once the selective monoprotonation occurs to generate intermediate **12**, a rapid insertion of the vinylic Ni–C bond into the coordinated carbonyl would afford nickel alkoxide **13**.¹⁴ Further protonation of the Ni–O bond of this alkoxide would then afford the observed product. It is important to note that a single diastereomer was obtained in each of the cyclizations described in Table 1. The reversibility of each of the steps proposed in the mechanism outlined is unclear, although the conversion of intermediate **12** into nickel alkoxide **13** is likely irreversible. Thus, either the kinetic selectivity of binding to the two prochiral faces of the carbonyl in **12** or the kinetic selectivity for the carbonyl insertion from rapidly equilibrating diastereomers of **12** is likely responsible for governing the reaction diastereoselectivity. As depicted in Scheme 3, if each mechanistic step proceeds with conservation of the overall skeletal conformation, there is a direct correlation of metallacycle conformation with observed reaction diastereoselectivity. Although we have little insight into the accuracy of this model, it has nonetheless served as an excellent predictor of stereochemistry when examining new substrate classes (vide infra).

Upon developing this working model for the reaction mechanism, it became apparent that much chemistry of the nickel

Table 2

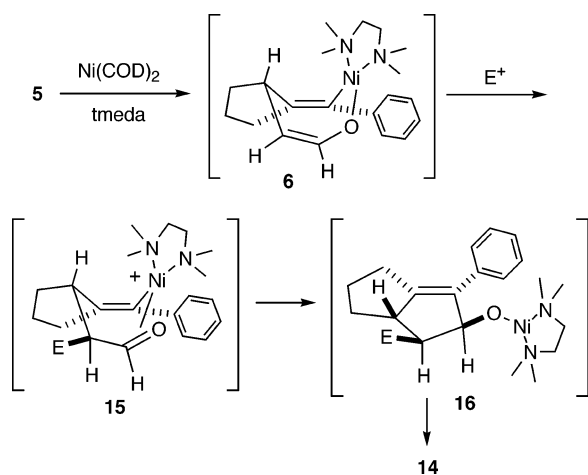
entry	electrophile	product (% yield)
1		68 %
2		72 %
3		68 %
4		82 %
5		80 %
6		72 %
7		72 %

enolate motif beyond simple protonations could potentially be developed. Using the structurally established metallacycle **6** as a test case, we examined a variety of tandem processes involving enolate alkylation (Table 2).¹⁵ Upon in situ generation of metallacycle **6** followed by treatment with reactive electrophiles, functionalized bicyclooctenols **14** were again obtained, with incorporation of the electrophilic unit at the expected position. Alkylations with methyl iodide, allyl iodide, and benzyl iodide proceeded efficiently to produce single diastereomers of the

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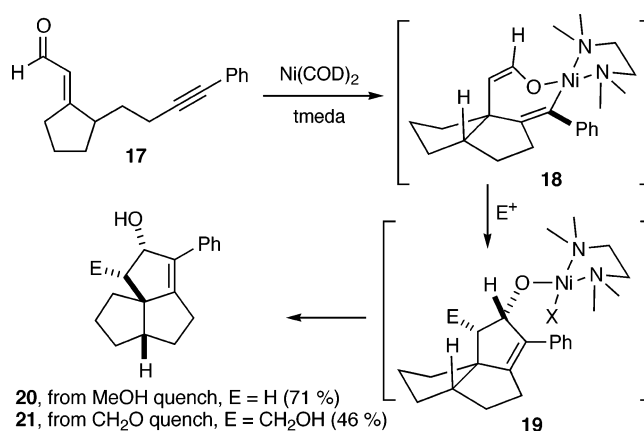
Scheme 4



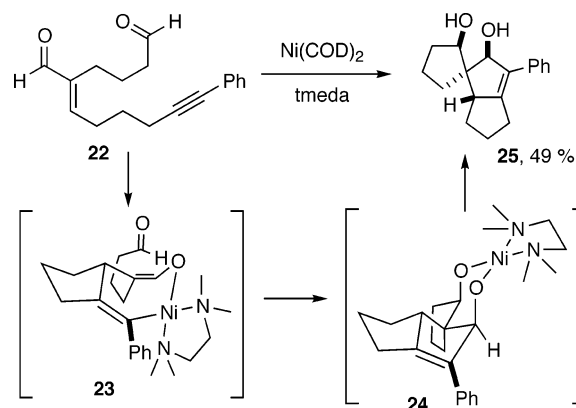
bicyclooctenols that bear three contiguous stereocenters (entries 1–3). Aldol reactions were also very efficient (entries 4 and 5). Quenching metallacycle **6** with benzaldehyde or formaldehyde afforded the expected aldol adducts in excellent yield as single diastereomers. The benzaldehyde-trapping example (entry 4) provides a particularly good illustration of the potential for rapid complexity generation by this process, because a simple acyclic achiral precursor is converted into a bicyclic product with four contiguous stereocenters and a synthetically versatile 1,3-diol unit in a single synthetic operation. Metallacycle **6** underwent efficient acylations, as demonstrated by quenching with benzoyl chloride to afford a β -hydroxy ketone (entry 6). This central metallacycle also participated in a Michael reaction with acrolein to generate a tricyclic lactol as a mixture of two diastereomers that were epimeric at the lactol center (entry 7). Again considering the mechanistic model presented above, metallacycle **6** likely undergoes exo-selective alkylation to afford intermediate **15**, followed by rapid insertion of the carbonyl to afford nickel alkoxide **16** (Scheme 4). Protonation of this alkoxide upon workup would afford the observed products, with all stereocenters being selectively generated (and correctly predicted) from the initial metallacycle conformation. At this point, we have little insight into the basis for the highly selective anti aldol reaction which presumably proceeds via an open transition state. The reactions described in Table 2 may be classified as alkylative [3+2] cycloadditions with the electrophile being incorporated at the central carbon of the three-carbon enone-derived unit.

The generality and scope of enolate alkylations within a metallacycle framework encouraged us to pursue the synthesis of more elaborate structures. To examine the participation of trisubstituted alkenes that would afford tricyclic products with a quaternary center, precursor **17** was prepared (Scheme 5).¹⁶ Enal **17** was treated with $\text{Ni}(\text{COD})_2/\text{tmeda}$ (1:1) in THF for 2 h at room temperature, and the resulting mixture was quenched with methanol. Despite the additional steric demands of this substrate, the cyclization proceeded efficiently to produce triquinane **20** as a single diastereomer in 71% yield. In analogy to the mechanistic proposal described above, the reaction likely proceeds by oxidative cyclization to afford metallacycle **18**. Enolate protonation upon workup with methanol, followed by carbonyl insertion, would afford nickel alkoxide **19**. Further

Scheme 5



Scheme 6



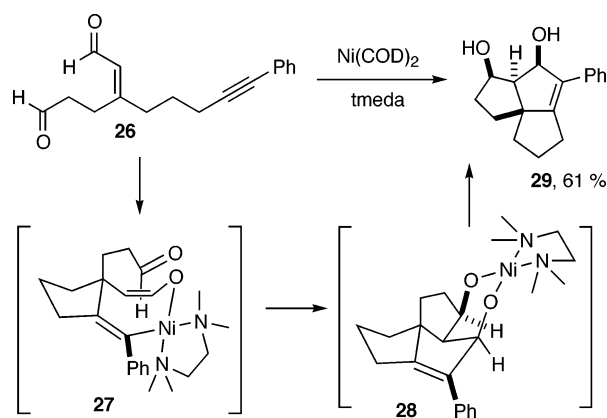
protonation of **19** would then afford the observed diastereomer of **20**. An aldol addition of enolate **18** to formaldehyde was also attempted, and diol **21** was obtained in 46% yield as a single diastereomer.

Fully intramolecular variants of the metallacycle formation/enolate alkylation cascade provide access to even more highly functionalized polycycles from acyclic precursors. To examine the feasibility of a complex cyclization of this type, cyclization precursors were synthesized with the enal, alkyne, and aliphatic aldehyde all tethered within a single compound. For instance, dialdehyde **22** was prepared by conventional procedures,¹⁶ and treatment with $\text{Ni}(\text{COD})_2/\text{tmeda}$, followed by aqueous workup, afforded spirocycle **25** in 49% yield as a single diastereomer (Scheme 6). In analogy to the intermolecular variants described above, the mechanism likely involves chemoselective oxidative cyclization of the enal and alkyne units to afford metallacycle **23**. Diastereoselective intramolecular aldol addition via an open transition state would afford nickel bis-alkoxide **24**, and aqueous workup would provide the observed product **25**.

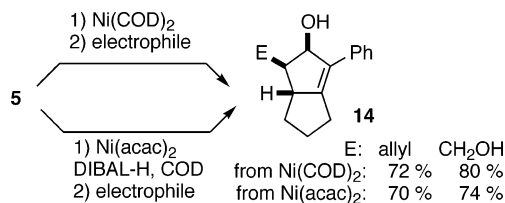
In a similar fashion, dialdehyde **26** was treated with $\text{Ni}(\text{COD})_2/\text{tmeda}$ followed by methanol workup to afford product **29** as a single diastereomer in 61% isolated yield (two-step yield from the diol, Scheme 7). Chemoselective oxidative cyclization in this instance would afford metallacycle **27**, followed by intramolecular aldol addition to afford nickel bis-alkoxide **28**, which produces compound **29** upon workup. The production of compounds **25** and **29** illustrates the potential for truly complex polycyclizations that rely upon the transient generation and alkylation of a transition metal enolate. It is significant to note that this novel procedure allows completely selective aldol

(16) See Supporting Information for complete experimental details.

Scheme 7



Scheme 8



couplings of nonequivalent aldehydes¹⁷ in both the inter- (Table 2, Scheme 5) and the intramolecular (Schemes 6 and 7) sense.

A drawback of these cascade, nickel enolate-mediated cyclizations is the requirement for stoichiometric nickel. Numerous attempts to devise efficient catalytic processes were unsuccessful. Zn^0 dust was an obvious choice, but efficient turnover rates were not observed with this additive. Nucleophilic reducing agents such as silanes and organozincs were not tolerated due to chemoselectivity issues. We previously reported the nucleophilic participation of reducing agents of this type in simpler coupling processes,⁸ and these reagents resulted in premature termination of the desired cascade cyclization event. Given the complexities associated with attempts to devise an efficient catalytic process, we examined the use of inexpensive $\text{Ni}(\text{II})$ precursors for the stoichiometric transformation. Following Mackenzie's preparation for generation of $\text{Ni}(\text{COD})_2$ from $\text{Ni}(\text{acac})_2$,¹⁸ we examined cascade reactions with the species generated by in situ reduction of $\text{Ni}(\text{acac})_2$ with DIBAL-H in the presence of cyclooctadiene. This modified procedure afforded results very similar to those obtained with stoichiometric

$\text{Ni}(\text{COD})_2$ while substantially lowering the cost. As an added advantage, glovebox manipulations were avoided because $\text{Ni}(\text{acac})_2$ is completely air stable. In two test cases involving allylation and formaldehyde aldol addition to the metallacycle derived from aldehyde **5**, yields of $\text{Ni}(\text{acac})_2/\text{DIBAL-H}$ -promoted reactions were only slightly lower than those of $\text{Ni}(\text{COD})_2$ -promoted reactions (Scheme 8).

Conclusions

The oxidative cyclization of enals or enones and alkynes with $\text{Ni}(0)$ provides a novel class of well-defined late transition metal enolates. These nickel enolates exist as the η^1 oxygen bound tautomer, and they undergo alkylations with a broad range of electrophiles including alkyl halides, aldehydes, enals, and acyl chlorides. A cascade cyclization process that involves the generation and alkylation of nickel enolates has been developed, and the overall transformation provides access to novel reductive or alkylative [3+2] cycloadditions. The cascade process may be accessed in either a partially or a fully intramolecular sense, and a noteworthy feature is the opportunity to carry out selective aldol reactions between nonequivalent aldehydes.¹⁷ The production of compounds **25** and **29** (Schemes 6 and 7) via the fully intramolecular version illustrates the potential for truly complex polycyclizations that rely upon the transient generation and alkylation of a transition metal enolate. In contrast to "poly-Heck cyclizations" which often involve the iterative incorporation of several alkenes or alkynes in essentially identical fashion, the fully intramolecular polycyclizations described herein involve fundamentally different chemical operations at each stage of the cascade process. For instance, the production of compounds **25** and **29** involves an oxidative cyclization of a $\text{Ni}(0)$ bis- π -complex, intramolecular aldol addition, insertion of an alkenyl nickel species into an aldehyde, and ultimately protonation of a nickel bis-alkoxide. The differential reactivities of the various nickel-carbon and nickel-oxygen bonds generated during this cascade sequence are critical to the overall chemoselectivity of the process. We anticipate that the developments described herein will suggest future directions for the involvement of transition metal enolates in cascade processes.

Acknowledgment. We acknowledge support for this research from NSF grant CHE-0093048.

Supporting Information Available: Full experimental details, copies of ^1H NMR spectra of all new compounds, and copies of X-ray crystallographic data (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA037423W

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